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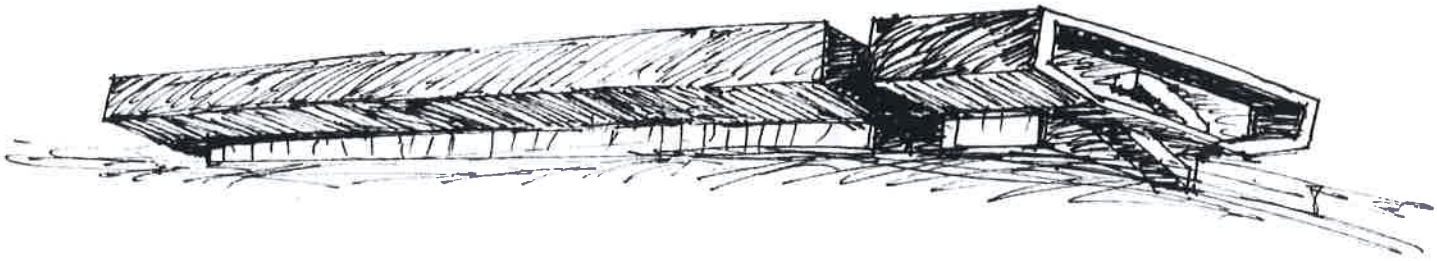
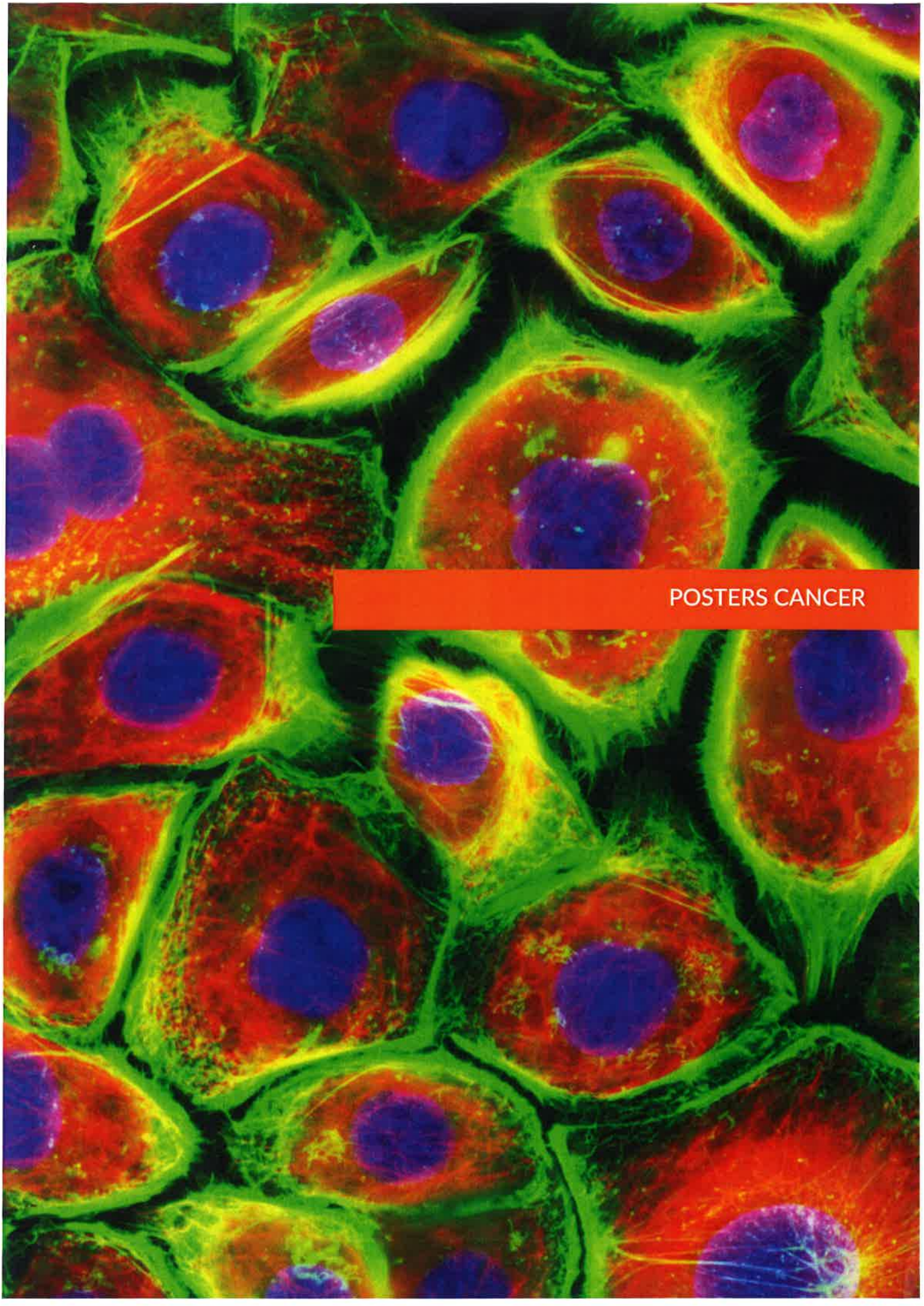


ABSTRACT BOOK



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Synthesis, screening and evaluation of the activity of new p53 activators in human tumour cell lines

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Strategies to increase p53 activity are of major interest for cancer therapy, considering the central role of this tumour suppressor protein in the regulation of DNA damage response, cell cycle arrest and apoptosis [1-3]. The activation of *wt* p53 and/or of its targets could result in increased cell cycle arrest and cell death, ultimately abrogating tumour development. The aim of the present work was to synthesize new p53 activators and further confirm their activity in a yeast p53 assay and in human tumour cell lines.

A series of chalcones was synthesized by Claisen-Schmidt condensation of a 2'-hidroxyacetophenone with appropriately substituted benzaldehydes by microwave irradiation. Using the yeast p53 assay, this series of chalcones was screened for p53 activity, which allowed the identification of eight potent p53 activators.

These chalcones were selected to be further studied in a panel of four human tumour cell lines in order to confirm their *in vitro* cell growth inhibitory activity. The mechanism of action of the two most potent compounds was further investigated in the non-small cell lung cancer cell line NCI-H460 (in which the compounds were quite potent). Results confirmed that both compounds reduced NCI-H460 viable cell number and cellular proliferation. In addition, alterations in the cell cycle profile and/or induction of apoptosis were observed following treatment with the compounds. Moreover, these compounds were shown to increase the cellular expression levels of *wt* p53 and of its transcriptional target p21, further indicating that they are p53 activators.

In conclusion, the present work describes the synthesis of eight new chalcones. Among the synthesized compounds, two were found to be p53 activators when using a yeast p53 assay. Both compounds increase p53 and p21 expression levels in human tumour cell lines. Additional studies are needed to prove the potential of these molecules in human tumour xenograph models in mice.

REFERENCES

[1] Khoo *et al.* (2014) Nat.Rev Drug. Discov. 13:217–236

[2] Amundson *et al.* (1998) Oncogene 17: 3287-99

[3] Athar *et al.* (2011) Curr. Pharm. Des. 17: 631-9

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